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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,783	01/16/2004	Mark W. Sleeman	REG 145A	6321

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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,783	SLEEMAN, MARK W.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Claims 1-10 in application submitted on 16 January 2004 are pending. Claims 1-10 are currently under examination.

Objections

Specification:

The disclosure is objected to because of the following informalities: there is a grammatical error on page 2, paragraph 0010. The line should read "factors", instead of factor". There is a typographical error on page 2, paragraph 0012, last line. The line should read "fasting" instead of "fasating". Appropriate corrections are required.

Claims:

Claims 3 and 8 contain the trademark/trade name Axokine. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a modified CNTF and, accordingly, the identification/description is indefinite. Appropriate correction is required.

Claim Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 is drawn to "a method of treating liver steatosis". However, the recited method step is directed to administering "an agent capable of activating a ciliary neurotrophic factor (CTNF) receptor". Thus, the method step does not match the goal set forth in the preamble, so it is unclear what the claim is directed to. Adding a phrase to the effect "such that liver steatosis is treated" would be remedial. Furthermore, the claim recites "a subject" without further defining the patient population.

Claims 2-5 are included in this rejection since they depend from claim 1 and do not resolve all the indefiniteness issues.

Claim 6 recites "a method of improving liver steatosis" and "such that liver steatosis is improved". It is unclear if the claim is directed to increasing the amount of fatty deposits in the liver, or to treatment of liver steatosis. Adding a phrase to the effect "a method of treating liver steatosis" and "such that liver steatosis is treated" would be remedial. Furthermore, the claim recites "a subject" without further defining the patient population.

Claims 7-10 are included in this rejection since they depend from claim 6 and do not resolve all the indefiniteness issues.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of treating liver steatosis comprising administering CNTF or Axokine ($CNTF_{Ax15}$) wherein liver steatosis results from diabetes or diabetes-related obesity, does not reasonably provide enablement for a method comprising administering administering any agent or modified CNTF to a subject wherein liver steatosis is results from alcohol consumption, exposure to hepatoxin or is of unknown etiology. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

The claims of the instant invention are drawn to treating liver steatosis in a subject in need thereof by administering an agent capable of activating CNTFR (Claims

1 and 6), wherein the agent is CNTF or a modified CNTF (Claims 2 and 7) and wherein liver steatosis results from alcohol consumption, obesity, and/or exposure to hepatotoxin.

The art recognizes that liver steatosis may have many causes including: (a) toxic factors, such as alcohol, drugs, (among them, corticosteroids, chemotherapeutic agents, high doses of tetracycline) and toxic substances (such as chloral carbohydrates, yellow phosphorus, cocaine); (b) nutritional factors (among them obesity, pancreatic disease, total parental nutrition); (c) endocrine and metabolic diseases such as diabetes mellitus, acute fatty liver of pregnancy, hemochromatosis (2000, Mach T. Med Sci Monit. 6:209-216, Table 1, page 210). In addition, viral infections, such as hepatitis B, C and HIV may lead to steatosis (2002, Tien et al. Semin Gastrointest Dis. 13:47-54, abstract). The specification discloses that a suitable subject for treatment by the methods of the instant invention is a mammal "suffering from or at risk from suffering from liver steatosis. Contributing factor(s) may include obesity and/or alcohol abuse...." (page 2, paragraph 0011).

Many CNTF-related neurotrophic factors are described in the art. Gluogan et al (1997, PNAS 94:6456-6461) teach recombinant CNTF and a CNTF mutation (page 6456, column 1 paragraph 3); Fandl et al. (2002, US Pat 6,472,178 B1) teach a number of modified CNTF molecules with improved biological activities (column 4 line 59-bridging column 5 lines 1-24). The specification discloses an "agent capable of activating the CNTF receptor" (page 2, paragraph 006).

The specification teaches only the use of one of the modified CNTF molecules, Axokine ($CNTF_{Ax15}$), in the methods of the instant invention (Figures 1 and 2, page 4, paragraph 0017). All of the working examples disclosed in the specification of the instant invention recite only Axokine ($CNTF_{Ax15}$) (Examples 2-8). The specification does not disclose the use of any other CNTF molecule in the methods of the instant invention. Furthermore, the specification discloses that Axokine "exerts metabolic effects that substantially contribute to the marked improvements in glucose and lipid homeostasis in diabetic mice" (page 4, paragraph 0017) but do not disclose the use of any other models of steatosis, such as the ob/ob mouse, the dietary methionine/choline-

deficient model, transgenic mouse models, carbon tetrachloride treated animals; furthermore, all the working examples recite the use of the db/db mouse model.

Thus, the specification and working examples teach only the use of Axokine in the treatment of liver steatosis in the db/db mouse model. The skilled artisan would have to undertake undue experimentation to determine which other of the CNTF-like molecules described in the art could be utilized in the methods of the instant, claimed invention and whether administration of CNTF-like molecules could be used to treat steatosis of etiologies such as alcohol consumption, non-diabetic obesity or exposure to hepatotoxin.

Due to the large quantity of experimentation necessary to identify which of the CNTF-like molecules could be used in the claimed methods, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to CNTF-like molecules other than Axokine and models other than the db/db mouse model, the complex nature of the invention, the state of the prior art, and the breadth of the claims which recite the use of any agent which activates CNTFR and multiple causes of liver steatosis, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gloaguen et al. (1997, PNAS 94:6456-6461). Claim 1 recites a method comprising administering an agent capable of activating a ciliary neurotrophic factor (CNTF) receptor and is directed to "A method of treating liver steatosis" in a subject in need thereof. Claim 2 recites the additional limitation of the agent being CNTF or a modified CNTF. Claim 5 recites "wherein liver steatosis results from alcohol consumption, obesity, and/or exposure to hepatotoxin".

Gloaguen et al. teach administration of CNTF and the variant DH-CNTF to genetically obese mice and mice with diet-induced obesity (page 6457, column 1, last paragraph and page 6458, figure 2). The reference is silent with respect to the presence of fatty liver condition in the ob/ob mouse. However, the art recognizes that the ob/ob mouse provides a well-characterized model of hyperinsulinemia and insulin-resistance in which hepatic steatosis develops spontaneously (see for example, Lin et al. 2000, Nature Medicine 6:998-1003, page 1001, column 1, last paragraph, bridging column 2, 1st paragraph). While the reference does not explicitly teach the presence of fatty liver condition in the ob/ob mouse, case law has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Also, case law has established that a compound and all of its properties are inseparable, as are its processes and yields (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, absent evidence to the contrary, the prior art discloses exactly what is claimed in the instant application. Once the CNTF is administered to the ob/ob mouse, as taught by Gloaguen et al, it has a necessary and inherent effect on the liver steatosis. Thus, Gloaguen et al. anticipates all the elements of claims 1, 2 and 5.

Claim 3 is rejected under 35 U.S.C. § 102(a) as being anticipated by Fandl et al. (US Patent 6,472,178, issued 29 October 2002). Claim 3 is drawn to administration of Axokine™. Axokine™ is identified in the art as $CNTF_{Ax15}$, a second generation CNTF

analog (Bluher et al. 2004, Diabetes 53:2787-2796, abstract). Fandl et al. teach the administration of CNTF variant, AX15, to ob/ob mice as a method to treat obesity (Column 37, Example 13). While the reference does not explicitly teach the presence of fatty liver condition in the ob/ob mouse, and use of $CNTF_{Ax15}$, to treat steatosis, case law has established that a compound and all of its properties are inseparable as are processes and their yields (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Once Axokine is administered to the ob/ob mouse, as taught by '178 reference, it has a necessary and inherent effect on the liver steatosis. Therefore, absent evidence to the contrary, the prior art ('178 patent) discloses exactly what is claimed by claim 3 in the instant application.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable in light of Gloaguen et al. (1997, PNAS 94:6456-6461) in view of Nongaki et al. (1996, Am J Physiol 271:E521-528). The teachings of Gloaguen et al. are outlined in detail above. The art recognizes, as discussed above, that the ob/ob mouse provides a well-characterized model of hyperinsulinemia and insulin-resistance in which hepatic steatosis develops spontaneously. Gloaguen et al. do not teach a method wherein treatment results in one or more of improved liver function determined by ALT/AST ratio, reduced stearyol-CoA desaturase-1 (SCD-1) gene expression or activity, enhanced the biochemical responsiveness of liver to insulin and/or reduced synthesis of complex lipids. Nongaki et al. teach administration of CNTF to intact rats. The

reference teaches that administration of CNTF stimulated lipoloysis, which would be a result of concomitant reduction in synthesis of complex lipids (page E521, abstract). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the administration of CNTF taught by Gloaguen et al. with the measurement of lipolysis taught by Nonogaki et al. The person of ordinary skill in the art would have been motivated to make that motivation because Gloaguen et al. teach that CNTF causes weight loss in experimental animals (page 6456, column 1, 1st paragraph) and it is well known in the art that weight loss is accompanied by lipolysis. One would reasonably have expected success because methods of measuring lipolysis are well known in the art and taught by Nongaki et al.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

SHS